ORIGINAL INVESTIGATIONS

Possibilities of screening for a high-risk axial skeletal lesion in psoriatic arthritis

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Objective: *to determine a set of signs that are prognostically significant for identifying a high-risk axial skeletal lesion in early psoriatic arthritis (ePsA).*

Patients and methods. *Examinations were made in 95 patients (47 men and 48 women) with peripheral arthritis lasting for I2 years, who met the 2006 Classification Criteria for Psoriatic Arthritis (CASPAR). The clinical characteristics of the patients were presented in our previously published work. In all the patients, a standard examination was made and the signs of inflammatory back pain (IBP) were identified according to the Assessment of SpondyloArthritis International Society (ASAS) criteria, the presence of human leukocyte antigen B27 (HLA-B27) was determined, and pelvic bone X-ray was done; regardless of whether they had IBP, 79 patients underwent magnetic resonance imaging (MRI) of the sacroiliac joints using a low-field Signa Ovation 0.35 T. Sacroiliitis (SI) diagnosed based on radiography (rSI) was considered reliable if there were bilateral changes corresponding to at least Stage II or unilateral changes corresponding to at least Stage III according to the Kellgren system. SI diagnosed based on MRI (MRI-SI) was regarded as active when osteitis was detected in the STIR mode in the bones adjacent to the joint on at least two slices or in the presence of two signals in a slice. X-ray and MRI results were assessed by an independent radi ologist. The extent of a skin lesion was determined from the body surface area (BSA): the extent was regarded insignificant, moderate, and significant with involvements of <3%, 3–10%, and >10%, respectively.*

The patients were divided into two groups. Group 1 included 65 (68.4%) patients with the manifestations of axial PsA (axPSA): IBP, and/or rSI, and/or MRI-SI; Group 2 consisted of 30 (31.6%) patients without axial manifestations, only with peripheral PsA (pPsA). Multivariate stepwise discriminant analysis was used to identify a group of signs that were most characteristic of axPsA.

Results and discussion. *Comparative analysis of the two groups showed that there were more males among patients with axPsA than among those with pPsA (39 (60%) and 8 (26.7%), respectively) (p=0.003). HLA-B27 positivity was also more often detected in patients with axPSA than in those with pPsA (30 (46.6%) and 7 (23.3%) patients, respectively) (p=0.02). In the axPSA group, there were significantly more individuals with moderate and high DAS, high CRP levels, and a more severe skin lesion (BSA >3%).*

The investigators obtained the following discriminant classification rule associated with axPSA: ***1.566 (if CRP is >5 mg/L) + 0.957 (if HLA-B27 is positive) + 0.986 (if BSA is >3%) + 1.845 (if DAS is moderate or high) + 0.6 (if the sex is male) >3.751 (p=0.0025).***
The sensitivity and specificity of the model were 68% and 73%, respectively.

Conclusion. *The combination of signs, such as male sex, HLA-B27 positivity, high or moderate DAS, CRP >5 mg/L, the extent of skin lesions according to BSA >3%, is prognostically significant for identifying high-risk axial skeletal lesion in ePSA. The proposed mathematical model can be used to screen patients for the early diagnosis of an axial lesion in ePSA.*

Keywords: *risk for axial lesion; early psoriatic arthritis; screening.*
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Various authors have reported that axial involvement in psoriatic arthritis (PsA) varies from 25 to 70% [1, 2]. Such a wide range of data is due to the fact that to date, there is no generally accepted international definition of axial PsA (axPsA), nor a unified approach to its diagnosis. The low percentage of identified axial involvement in PsA is an urgent problem not only in the Russian Federation but all over the world due to the following factors:

- possible subclinical (pain-free) course of axial involvement [3];
- lack of clear diagnostic criteria for axial psoriatic arthritis [2];
- lack of accepted international guidelines for visualization of axial structures in PsA patients;
- low awareness among clinicians;
- lack of simple and affordable screening methods in real clinical practice.

According to international treatment recommendations for PsA [4, 5], axial involvement is of independent significance for the choice of therapy. Basic synthetic anti-inflammatory drugs successfully used in the peripheral arthritis are ineffective when the axial skeleton is involved in the inflammatory process [5]. In the case of axial involvement and low effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs), it is recommended to immediately prescribe biologic disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor-alpha inhibitors, or interleukin-17A

inhibitors [5]. In addition, there are reports about a more severe course of PsA involving the axial skeleton compared to peripheral joint involvement only, [2, 6] which underscores the importance of axial PsA detection by rheumatologists in order to promptly select appropriate therapy. This problem is of great social significance due to high axial involvement in young male patients and its negative impact on their ability to work. Thus, a delay in diagnosing axial involvement in early PsA (ePsA) is highly undesirable. Today there are no unbiased screening methods to determine a high risk of axial involvement in PsA.

The purpose of the study was to evaluate a set of features that are prognostically significant in detecting a high risk of axial involvement in ePsA.

Patients and Methods. The study included 95 patients: 47 men and 48 women diagnosed with PsA in accordance with the CASPAR criteria (ClASsification criteria for Psoriatic ARthritis, 2006), having a history of peripheral arthritis for ⩽2 years; the clinical characteristics of patients in this cohort have already been presented [7]. Patients with back/neck pain or limited spinal mobility were not specifically selected. PsA activity was evaluated by the DAS index. PSA activity was considered low at DAS >1.6 to ⩽2.4, moderate at DAS >2.4 to ⩽3.7, high at DAS >3.7, and remission was determined at DAS <1.6. All patients underwent a standard clinical examination. A targeted survey revealed signs of inflammatory back pain (IBP) according to the ASAS criteria (Assessment of SpondyloArthritis international Society) [8], if any. All patients underwent a standard pelvic x-ray examination. Radiographic sacroiliitis (rSI) was diagnosed if there were changes corresponding to the modified New York criteria: bilateral Kellgren stage II or higher, or unilateral Kellgren stage III or higher. Seventy-nine patients, regardless of the presence of IBP, also had MRI scanning of the sacroiliac joints (SIJ) performed on a low-field MRI scanner Signa Ovation 0.35 T. MRI-SI was considered active when the STIR mode revealed an area of bone marrow edema (BME) in the bones adjacent to the joint, at least on two consecutive scans, or if there were ⩾2 BME areas on one scan. Ninety-three patients had serological typing of the HLA-B27 antigen with a polymerase chain reaction test. The skin lesion was estimated by Body Surface Area (BSA): involvement of <3% of the skin was considered insignificant, 3–10% – moderate, and >10% – extensive.

The patients were assigned to one of the two groups for a comparative analysis: Group 1 included 65 (68.4%) patients with axial involvement (axPsA): IBP and/or rSI and/or MRI-SI; group 2 included 30 (31.6%) patients without axial involvement (peripheral PsA (pPsA) only).

Multivariate stepwise discriminant analysis was used to identify a group of features that are most characteristic of patients with axPsA. The calculation was performed using the Microsoft Excel and the statistical data analysis software package Statistica 10 for Windows (StatSoft Inc., USA).

Results. There were significantly more male patients in the axPsA group than in the pPsA group: 39 (60%) and 8 (26.7%), respectively (p=0.003). The positive HLA-B27 status was also more frequent in axPsA than in pPsA: in 30 (46.6%) and 7 (23.3%) patients, respectively (p=0.02). The activity of the disease was significantly higher in axPsA than in pPsA: moderate and high DAS activity was detected in 64 (98.5%) and 22 (73.3%) patients, respectively (p=0.015).

In axPsA, the level of CRP exceeded 5 mg/L significantly more often than in individuals without axial involvement: in 89.2% and 63.3% of cases, respectively (odds ratio, OR 4.80; 95% confidence interval, CI 1.63–14.13; p=0.004).

Moderate skin lesions (BSA >3%) were significantly more frequently detected in the axPsA group than in the pPsA group: in 24 (40.7%) of 59 and in 4 (14.8%) of 27 patients, respectively (OR 3.94; 95% CI 1.21–12.86; p=0.023).

It is a combination of features – male sex, HLA-B27 positivity, mild or high activity of peripheral arthritis according to DAS, CRP > 5 mg/L, and skin lesion (BSA) > 3% – that constitutes a clinical predictor for detecting patients with a high risk for the development of axial involvement in ePsA.

The following discriminant classification rule associated with axPsA was created: **1.566 (if CRP >5 mg/L) + 0.957 (if HLA B-27 detected) + 0.986 (if BSA >3%) + 1.845 (if DAS activity is moderate or high) + 0.6 (if male) >3.751 (p=0.0025**; see Table and Figure) The model sensitivity was 68%, and the specificity was 73%.

For immediate assessment of a high risk of axial involvement in ePsA, the following is to be determined: CRP level, HLA-B27

Stepwise discriminant analysis associated with axPsA

Parameter, points	Classification function			
	no axial lesion	axial lesion	discriminant coefficient (weighting factor)	p
CRP >5 mg/L – 1 CRP <5 mg/L – 0	3.072	4.638	1.566	0.038
HLA B-27 (+) – 1 HLA B-27 (-) – 0	0.331	1.288	0.957	0.107
BSA >3% – 1 BSA <3% – 0	0.902	1.888	0.986	0.118
DAS moderate to high activity – 1 DAS low activity – 0	13.163	15.008	1.845	0.098
Gender, male – 1 Gender, female – 0	3.369	3.969	0.600	0.3
Constant	8.057	11.808	3.751	

status, skin lesion area (BSA), DAS disease activity index, the patient's gender. Based on the data obtained, the indicator «Y» is calculated using the formula:

$$Y = 1.566 \times X_1 + 0.957 \times X_2 + 0.986 \times X_3 + 1.845 \times X_4 + 0.6 \times X_5,$$

where: X_1 = CRP level (mg/L): if CRP is >5 mg/L, 1 point is given, if CRP is ⩽5 mg/L, 0 points; X_2 = the presence of the HLA-B27 antigen: if HLA-B27 is detected, 1 point is given, if not, 0 points; X_3 = the BSA skin lesion area: if BSA is >3%, 1 point, if ⩽3%, 0 points; X_4 = DAS disease activity: if moderate or high (DAS>2,4), 1 point, if low or remission, 0 points; X_5 = patient's gender: if male, 1 point, if female, 0 points. If Y >3.75, a high risk of axial involvement in ePsA is determined.

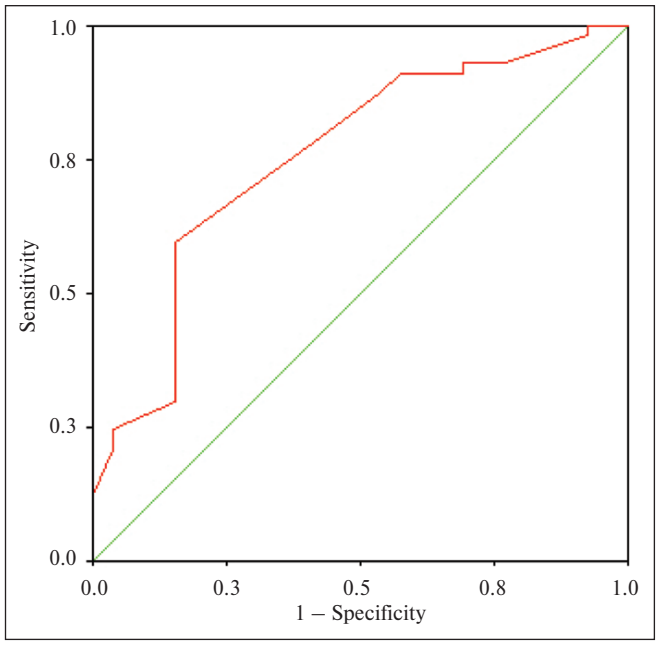
There were other significant differences between the axPsA and pPsA groups: patients with axPsA were younger, had a shorter duration of arthritis, and their values of disease activity and subjective pain assessment on the visual analog scale (VAS) were significantly worse than in patients without axial involvement. [7] However, when using multivariate stepwise discriminant analysis, these signs turned out to be prognostically insignificant for diagnosing axial involvement.

Discussion. Diagnosing axial involvement in PsA requires a comprehensive examination, including targeted detection of IBP and visualization of axial structures.

ASAS criteria help detect IBP. [8] However, 25% of PsA patients with axial involvement have no IBP [7, 9]. More than a half of PsA patients (55.6% to 60.3% according to our data) diagnosed with IBP, had it episodically, and it was assessed as weak [4, 7], often localized only in the cervical spine [4]. Patients do not always report such kind of neck/back pain to their doctors [4]. Some authors believe that IBP in axPsA only meets the ASAS criteria when the disease is highly active: back pain ⩾4 according to VAS, and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) ⩾4, despite the use of NSAIDs [10]. Therefore, IBP is not a reliable sign of the axial skeleton involvement in PsA, and the sensitivity of ASAS criteria of IBP is lower in axPsA than in ankylosing spondylitis (AS) [11]. It is not a coincidence that when examining large cohorts of PsA patients, IBP was detected only in 15% of cases [12]. Due to the characteristic feature of axPsA, i.e., a possible pain-free course of the axial disease, the existing diagnostic methods cannot be fully applied.

Since currently there is no consensus definition and diagnostic criteria of axPsA, various imaging techniques are used in the studies to confirm the axial involvement: SIJ x-ray (most common) [11], cervical and lumbar x-ray (rarely) [9]; some studies used SIJ MRI for ePsA [7]. Most authors [11] diagnose axial involvement if a patient has x-ray signs of reliable SI, i.e. corresponding to the modified New York criteria [13], although at least unilateral stage II SI is considered a marker of axial involvement in a number of studies [14]. Such approach to diagnosing SI in PsA patients seems rational to us. According to M. Haroon et al. [14], patients with axPsA more often have asymmetric SI which is characterized by less pronounced structural damage to SIJs. Of note, such an axPsA phenotype is associated with HLA-B*0801 rather than with HLA-B27. [14]

It is important to remember that reliable radiological changes in the SIJs are not formed at early stages of the disease.



ROC curve determines the sensitivity and specificity of the discriminant classification rule associated with axPsA. For the threshold of 3.711, the sensitivity of the model was 79%, and the specificity was 57.7%. Area under the ROC curve was 0.756 (95% CI 0.642–0.869)

RSI was detected in 44.6% of our patients with the axial involvement in early peripheral arthritis [4]. In addition, interpretation of radiological changes that characterize the early SI stages (stage II) is often difficult due to SIJ anatomy [15] and requires special expertise of a radiologist. It should also be taken into account that, unlike AS, in PsA damage to the spine is possible without SI (up to 33% of cases, according to D. R. Jadon et al. [9]), which requires additional cervical and lumbar radiographic and/or MRI evidence. Radiological changes in the cervical spine are also known to occur in approximately 70–75% of PsA patients, and this significantly exceeds the incidence of SI in such patients [16].

An axial lesion is diagnosed when at least one cervical and lumbar radiographic syndesmophyte /parasyndesmophyte is observed [9]. At the same time, it should be noted that damage to the posterior structures (narrowing and ankylosis of the zygapophysial joints), especially the cervical spine, is common and observed in 28% of cases [17]. Changes in the zygapophysial joints can also be detected in patients without syndesmophytes, which indicates axial involvement as well, although it is not always taken into account in diagnosing axPsA.

When discussing MRI detection of active inflammation in the SIJ area, one should remember that not all patients with axial lesions are diagnosed with osteitis, and not at all stages of the disease. We diagnosed active MRI SI in 43.1% of the patients who had axial involvement in ePsA [4]. According to L. Williamson et al. [18], active MRI SI signs in PsA do not correlate with the presence of IBP.

Thus, the complexity of diagnosing axial involvement in PsA and the necessity of a comprehensive approach to such patients are obvious. On the one hand, expert radiologists are

required to evaluate the results of an instrumental examination, and on the other hand, it requires expensive MRI equipment, which can be difficult to achieve in real clinical practice. In this regard, introduction of simple screening methods into clinical practice will facilitate the identification of PsA patients with a high risk of axial involvement, reduce the time of examination and contribute to timely and adequate therapy. The proposed mathematical model is an effective method for assessing a high risk of damage to the axial skeleton in patients with ePsA.

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Conflict of Interest Statement

The investigation has been conducted within the framework of scientific topic №398 «Pathogenetic features and personalized therapy of ankylosing spondylitis and psoriatic arthritis» and within the framework of technology «Clinical and instrumental characteristics of an axial lesion in psoriatic arthritis», approved by the Academic Council of the V.A. Nasonova Research Institute of Rheumatology. A patent for an invention was obtained according to the results of the study: Application №2020111499/14 (019384).

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